Novel cancer therapies: treatments driven by tumour biology

Ramya Ramaswami, Victoria Harding, Thomas Newsom-Davis

Department of Oncology,
Chelsea & Westminster
Hospital NHS Foundation Trust,
London, UK

Correspondence to

Dr Thomas Newsom-Davis,
Department of Oncology,
Chelsea & Westminster
Hospital NHS Trust,
369 Fulham Road,
London SW10 9NH, UK;
tom.newsom-davis@chelwest.
nhs.uk

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ABSTRACT

The traditional view is that treatments within oncology largely consist of chemotherapy, which aims to maximise damage to the rapidly dividing cancer cells but often at the expense of normal cells and overall quality of life for the patient. The development of anticancer drugs has changed from the serendipitous discoveries of the past, to today's purposeful targeting of cancer cells which takes advantage of novel technological developments and a greater understanding of tumour biology. The aim of these new treatments is to affect the essential function of the cancer cell while sparing normal cells, and limiting side effects. The phenotypic characteristics of tumours, such as unregulated growth signalling, development of new vascular systems and the evasion of immune destruction are used to identify potential drug targets. Here we review the clinical evidence and molecular mechanisms for novel therapies that are currently in use and those that are in development.

INTRODUCTION

Historically, it was thought that cancer cells were insular entities, self-proliferating independently of their environment. Subsequently however, it has been demonstrated that changes in the cancer cells and the local tumour microenvironment cause tumourigenic traits. Cancer is a heterogenous condition and so deciphering its biology is difficult. One view sees cancer as consisting of genetically erroneous and unstable cells that have a perpetual drive to proliferate and do not adhere to the usual regulatory mechanisms that would otherwise lead to normal cell death. Hanahan and Weinberg¹ amalgamated the features of tumour biology and defined the 'Hallmarks of cancer', which highlight the phenotypic characteristics of cancer cells in their capacity to grow, resist the usual mechanisms of cell death and invade (figure 1). Four of these hallmarks have been the main focus of drug development to date and will be explored here: inhibition of proliferative signals; targeting the vascular supply of the tumour (angiogenesis); exploiting the genomic instability of tumours; tackling immune evasion by the cancer cells and the ability of cancer cells to evade immune detection.

INHIBITION OF PROLIFERATIVE SIGNALLING

Normal cellular homeostasis is achieved by a complex network of cellular signals (figure 2). External growth signals instruct cells via their surface receptors, to grow, repair and divide. Intracellular pathways pass from the cell surface to the nucleus, and if there is no such signal received at the nucleus, cell growth and division cease. By contrast, cancer cells can stimulate their own

growth without these external signals. This occurs through three mechanisms: constitutive activation of cell surface receptors, overexpression of cell surface receptors and cancer cell release of its own growth signal.

The epidermal growth factor receptor (EGFR) family consists of a number of extracellular protein receptors which, upon activation by their ligand, can propagate downstream signalling and constitutive pathway activation (table 1). These signalling cascades are implicated in gene transcription for cell proliferation, angiogenesis and invasion. Inhibitors of EGFR pathways are a group of targeted therapies that interrupt these processes and have been shown to be important treatments in lung, breast and colorectal cancers.

Targeting EGFR

EGFR (ErbB-1) is an attractive signalling pathway target as it regulates many functions including cell proliferation, migration and angiogenesis. In colorectal cancer, the gene for EGFR is overexpressed in 60–80% of cases. In the CRYSTAL (Cetuximab Combined with Irinotecan in First-Line Therapy for Metastatic Colorectal Cancer) trial, cetuximab in combination with chemotherapy improved response rates compared with chemotherapy alone, with a HR of 1.40 (95% CI 1.12 to 1.77; $p=0.004$). This equated to a modest improvement in median overall survival (OS, 19.9 vs 18.6 months).^{2–3} Cetuximab is also recommended for use in conjunction with radiotherapy for patients with locally advanced squamous cell cancer of the head and neck (table 2). Combination treatment significantly prolongs progression-free survival, as well as increasing OS (49.0 vs 29.3 months, HR 0.74; $p=0.03$).⁴

The use of cetuximab has also led to greater knowledge regarding the link between Kirsten rat sarcoma (KRAS), a member of the RAS gene family, which is linked closely to the activity of EGFR. In the proportion of colorectal cancers in which there are KRAS mutations, there is a very poor response to anti-EGFR monoclonal antibodies as a result of activation of alternative signalling pathways. Consequently, the presence of a KRAS mutation is a predictive biomarker which is commonly tested in colorectal cancer patients to guide the possible use of EGFR targeted monoclonal antibodies.⁵

The identification of such biomarkers has revolutionised treatment in oncology. Nowhere is this better seen than in non-small cell lung cancer (NSCLC) where mutations in the kinase domain of EGFR have been found to correlate with impressive responses to EGFR tyrosine kinase inhibitors (TKI) such as gefitinib and erlotinib, and to be associated

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Figure 1 Hallmarks of cancer—adapted from Hanahan and Weinberg illustrating the phenotypic characteristics of cancer.

with a better overall prognosis. EGFR mutations occur in approximately 10–15% of all lung cancer patients, are most commonly found in those with adenocarcinoma histology and who do not smoke, and are now routinely tested for at

diagnosis.^{6–8} Advanced stage lung cancer patients with an EGFR mutation who receive erlotinib instead of platinum-based chemotherapy, have an improved progression-free survival (PFS, 9.7 vs 5.2 months (HR 0.37, 95% CI 0.25 to 0.54; $p < 0.0001$),

Figure 2 Cancer drug targets in cellular pathways.

Table 1 The epidermal growth factor receptor family

Receptor	Alternative name	Ligands	Licensed drugs
ErbB-1	EGFR	EGF, TGF- α , HB-EGF, amphiregulin, betacellulin, epigen, epiregulin	Gefitinib, erlotinib, afatinib
ErbB-2	Her2/c-neu	Homodimer (no ligand)	Trastuzumab, lapatinib, sunitinib, sorafenib
ErbB-3	Her 3	Neuregulin 1, 2	
ErbB-4	Her 4	HB-EGF, betacellulin, epiregulin, neuregulin 1,2,3,4	

EGFR, epidermal growth factor receptor; HB-EGF, heparin-binding EGF-like growth factor; TGF- α , transforming growth factor- α .

a significantly reduced risk of progression or death, and experience a favourable side effect profile.⁹ Similar benefits have been observed with gefitinib. Although no OS benefit has been demonstrated for these agents, this most likely reflects the

crossover design of the trials in which all patients receive an EGFR TKI at some stage in their treatment.

Targeting HER2

Amplification of the human epidermal growth factor receptor 2 (HER2) gene and subsequent overexpression of the HER2 receptor is noted in approximately 20% of breast cancers.¹⁰ In this population which is known to have a poorer outcome and worse response to conventional chemotherapy, the addition of trastuzumab, a humanised monoclonal antibody targeting HER2, to conventional treatment reduces the risk of disease recurrence by up to 46% and increases OS (HR 0.66, $p=0.0115$).¹¹ In advanced stage disease, the addition of trastuzumab to paclitaxel results in longer median times to disease progression compared with paclitaxel alone (11.8 vs 5.9 months; HR 0.60; $p<0.001$), however, median OS is similar in both groups (OS=26.7 vs 25.2 months; HR 0.88; $p=0.16$).¹²

Trastuzumab is also licensed as first-line treatment in combination with chemotherapy in HER2-positive gastric cancer, which is an aggressive tumour with poorer outcomes (table 2).

Table 2 Summary of targeted agents and licensed uses

Agent	Cancer Hallmark	Mode of Action	Site/Context	Common side effects	NICE Guidance
Panitumumab	Growth signalling	Monoclonal Abs EGFR	Colorectal—metastatic	Dermatological reactions, pulmonary complications, electrolyte disturbances	Not recommended as monotherapy
Trastuzumab	Growth signalling	Monoclonal Abs HER2	Breast—in early breast cancer or metastatic HER2 +++	Cardiotoxicity, allergic reaction, hypertension, neutropenia, diarrhoea, nausea and vomiting	Given at 3-week intervals for 1 year or until disease recurrence treatment option for women with early-stage HER2-positive breast cancer neoadjuvant or adjuvant
Trastuzumab	Growth signalling	Monoclonal Abs HER2	Gastric—in metastatic pts HER2 +++	Cardiotoxicity, allergic reaction, hypertension, neutropenia, diarrhoea, nausea and vomiting	Not recommended
Lapatinib	Growth signalling	TKI	Breast—in metastatic setting	Anorexia, headache, cardiotoxicity, diarrhoea	Not recommended
Cetuximab	Growth signalling	Monoclonal Abs EGFR	Colorectal+head/neck—both in first-line +metastatic	Dermatological reactions, electrolyte disturbance, anaphylaxis	In combination first line (with 5FU/folinic acid and oxaliplatin) when surgery carried out, mets only in liver, neoadjuvantly to shrink. In metastatic setting with irinotecan
Erlotinib/Gefitinib	Growth signalling	TKI	Lung—first-line in EGFR +pts and in second-line NSCLC	Dermatological reaction, diarrhoea, nausea	Use in first line in presence of EGFR mutation, and in the context of progression
Everolimus	Growth signalling	mTOR inhibitor	RCC—second-line treatment	Dermatological reaction, diarrhoea, nausea, loss of appetite	Use in metastatic/second line setting in RCC
Temsirolimus	Growth signalling	mTOR inhibitor	RCC—second-line treatment	Dermatological reaction, diarrhoea, nausea, loss of appetite	Use in metastatic/second line setting in RCC
Bevacizumab	Angiogenesis	Monoclonal Abs VEGF	Breast, colorectal, RCC, lung, ovarian, Brain—in metastatic setting	Hypersensitivity reaction, nausea, vomiting, high blood pressure, VTE, bleeding	Available for breast, brain and ovarian cancer on cancer drugs fund. Licensed for second-line use in metastatic colorectal cancer
Sunitinib	Angiogenesis	TKI	RCC—In first-line metastatic setting	Thyroid dysfunction, hypertension, diarrhoea, dermatological reaction	In first line metastatic setting
Sorafenib	Angiogenesis	TKI	HCC—In first-line metastatic setting	Diarrhoea, hypertension, sore mouth, dermatological reaction	Use in HCC in first line setting
Imatinib	Cell Proliferation	TKI	CML—First-line	Nausea, diarrhoea, fluid retention, neutropenia, rash, bleeding	Use in first line in CML
Vemurafenib	Cell Proliferation	TKI	Melanoma—metastatic setting	Arthralgia, skin rash, photosensitivity	In metastatic setting—those who express BRAF V600E mutation
Abiraterone	Cell Proliferation	Hormonal agent against CYP17	Prostate—metastatic setting	Hypokalaemia, hypertension, fluid retention	Recommended in refractory prostate cancer

CML, chronic myeloid leukaemia; EGFR, epidermal growth factor receptor; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; TKI, tyrosine kinase inhibitor; VEGF, vascular endothelial growth factor; RCC, renal cell carcinoma; HCC, hepatocellular carcinoma; NICE, National Institute of Health and Clinical Excellence.

The addition of trastuzumab improves OS by 2 months compared with standard therapy.¹³ Though this may seem like a small benefit, the identification of HER2 in gastric cancer is an important step forward in understanding the tumour biology of this difficult-to-manage disease.

Lapatinib, a HER2-specific TKI, inhibits signalling through the HER2 receptor through ligand-induced signalling blockade. Lapatinib appears to have a synergistic effect by causing accumulation of HER2 at the cell surface, thereby enhancing the effects of trastuzumab. Correspondingly, in HER2-positive metastatic breast cancer, the combination of lapatinib and trastuzumab is more effective than lapatinib alone in terms of PFS and response rate.¹⁴

Downstream signalling: mammalian target of rapamycin

Whereas the EGFR family provides anticancer drug targets at the cell receptor level, knowledge of cellular control downstream of this is equally important so that all key regulators of cell growth are explored. The mammalian target of rapamycin (mTOR) is a downstream molecule within the intracellular signalling pathway which regulates a variety of functions, including cellular growth, metabolism, proliferation and angiogenesis. Everolimus and temsirolimus are inhibitors of mTOR and are licensed in the treatment of metastatic renal cell cancer. Therapy in renal cell cancer was previously limited to toxic cytokine therapies, such as interferon- α and interleukin 2, however, when used in the context of relapsed disease, everolimus increases median PFS from 1.87 to 4.90 months compared with placebo.^{15 16} Everolimus is also being trialled in the context of metastatic breast cancer as it appears that targeting mTOR may be applicable to a range of tumour types.

TARGETING ANGIOGENESIS

Cancer cells are able to recruit new blood vessels to supply the necessary nutrients for tumour growth, a process termed neoangiogenesis, via the secretion of pro-angiogenic factors. All cells lacking in oxygen will produce a transcription factor (hypoxia-inducible factor, HIF), which stimulates the release of vascular endothelial growth factor (VEGF) that binds to the cell surface receptors (VEGF-receptor, VEGF-R) of nearby endothelial cells. This process results in formation of new blood vessels in the vicinity of the cell. Expression of VEGF is increased in a number of tumours including breast, lung and ovarian cancers, and often confers a poor prognosis. Over the past decade, exploring the angiogenesis hallmark and targeting the overexpression of VEGF by cancer cells has been an important development in novel anticancer therapy.¹⁷

VEGF inhibitors

Bevacizumab is a monoclonal antibody that inhibits all active isoforms of VEGF and which neutralises the ability of VEGF to bind to its receptor on endothelial cells. This results in the prevention of neovascular formation by pruning abnormal vessels and promoting tumour endothelial cells apoptosis, leading to decreased interstitial fluid pressures within the tumour and enabling enhanced delivery of oxygen and chemotherapeutic drugs. Bevacizumab is an attractive adjunct to standard chemotherapeutics in colorectal, breast and ovarian cancers. For example, in advanced colorectal cancer, bevacizumab can be used as a first-line option, and has been shown to improve PFS when added to chemotherapy in the first-line setting (10.4 vs 7.1 months, HR 0.62; $p=0.001$).^{18–20}

It has been suggested there is a particular role for bevacizumab in vascular tumours. In one such example, the primary

brain tumour glioblastoma multiforme (GBM) where the median survival from diagnosis is just 3–6 months, patients with recurrent disease were treated with bevacizumab and the chemotherapeutic agent irinotecan. In 20 of the 35 patients, there was a 30% decrease in size of the tumour, whilst 6 month OS was 77% (95% CI 64% to 92%).²¹

The effects of bevacizumab in the other tumour sites, such as breast, ovarian, renal cell and lung cancers have been mixed, but some benefit has been shown when compared to chemotherapy alone.¹⁸ The toxicity of treatment is important to consider and has been a subject of intense discussion between clinicians and drug regulatory bodies. The Food and Drug Administration (FDA) approved use of bevacizumab in GBM, colorectal, renal cell and metastatic HER2-negative breast cancer. However, despite accelerated approval for the latter, the overall benefits were subsequently deemed small in comparison to risks such as bleeding, venous thromboembolism and osteonecrosis of the jaw. As of November 2011, the FDA revoked its approval of bevacizumab in metastatic breast cancer, although it continues to be authorised in Europe. This emphasises the importance of carefully considering the balance between benefit and risk when developing novel targeted agents.

VEGF and multikinase inhibitors

Sunitinib and sorafenib are multitargeted receptor TKIs which affect the VEGF pathways and the tumour cell proliferation pathway of RAF/MEK/ERK (figure 2). By comparison with interferon- α in the treatment of metastatic renal cell carcinoma, sunitinib has demonstrated superiority in median PFS and in quality-of-life outcomes.²² Meanwhile, sorafenib has shown promise in those with advanced hepatocellular carcinoma by improving median survival and deterring radiological progression by approximately 3 months.²³ The inhibition of multiple pathways may seem attractive, however, side effect profiles are usually more pronounced and need to be taken into consideration. In the case of sunitinib and sorafenib, for example, these include rash, hypertension, thyroid dysfunction and diarrhoea (table 2).

TARGETING CHROMOSOMAL ABERRATIONS

Perhaps the best example of purposeful and rational design of an anticancer drug based on tumour biology is imatinib in the treatment of chronic myeloid leukaemia (CML). CML is well known for the Philadelphia translocation, which leads to a fusion between Ableson tyrosine kinase (Abl) at chromosome 9 and break point cluster (Bcr) at chromosome 22. The resulting oncogenic fusion gene, Bcr-Abl, encodes a constitutively active kinase and the cancer cell develops a dependency to the resulting product which is now required to propagate its malignant phenotype, a phenomenon known as 'oncogene addiction'. Imatinib inhibits Ableson kinase, directly affecting the switch that propagates the chronic phase of CML. The use of imatinib has revolutionised the treatment of CML, resulting in high rates of remission and an almost doubling of 5-years survival from 27.1% to 48.7% (post-imatinib).²⁴ Patients started on imatinib have a low risk of progression to accelerated phase or blast crisis (81% event-free survival at 8 years).²⁵

Other oncogenic fusion genes have been discovered, including echinoderm microtubule-associated protein-like 4 (EML4) and anaplastic lymphoma kinase (ALK) in NSCLC. EML4-ALK is an aberrant fusion gene that propagates cell proliferation and occurs in a small proportion of patients with NSCLC who tend to be young, non-smokers, with adenocarcinoma histology. Crizotinib, an ALK TKI, has shown very impressive response

rates and is now licensed for the treatment of relapsed, advanced-stage ALK-mutated NSCLC.^{26 27}

Another recent addition to this list of treatments targeting specific tumour mutations is identification of the V600E mutation in the BRAF gene, which is found in 40–60% of patients with metastatic melanoma. The introduction of vemurafenib, a potent inhibitor of mutated BRAF, has brought about a step-change change in the way the condition is managed. In the registration study, 6 months OS was 84% in the vemurafenib group compared to 64% in the control (dacarbazine chemotherapy) group.²⁸ These results have led to the introduction of routine BRAF mutation testing in the management of metastatic melanoma.

SYNTHETIC LETHALITY

Synthetic lethality is the concept that in the relationship between two genes, loss of one gene function is not lethal to the cell due to reliance on a second gene product, however loss of function of both results in cell death. This allows targeting of cancer cells which already carry an inherent mutation in one gene as they can now be killed through therapeutic inhibition of the other. Normal cells, which carry both normal genes, are spared cell death.

The best examples of this approach are poly(ADP-ribose) polymerase 1 (PARP1) inhibitors in (breast cancer) BRCA-1 or BRCA-2 mutation ovarian and breast cancer.²⁹ PARP is involved in repair of double-strand DNA breaks and, when inhibited, there is an over-reliance on the homologous recombination DNA repair pathway to maintain cellular integrity. BRCA mutation cancers are deficient in homologous recombination, and so, will be killed by PARP inhibition, whereas, normal cells should be unaffected. The PARP inhibitors iniparib and olaparib are undergoing clinical trials in BRCA-mutation cancers.

IMMUNOTHERAPY AND CANCER VACCINES

Although there have been innumerable attempts over the years to use the immune system in the treatment of cancer, results have largely been disappointing, with success limited to treatments such as intravesical *Bacillus Calmette-Guerin* (BCG) for localised bladder cancer.³⁰ By contrast, new immunotherapeutic approaches have begun to yield much more impressive results. Targeting cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), a key molecule that induces anergy and immune tolerance in antigen-specific T cells, has been a significant development in the treatment of stage IV melanoma.³¹ Ipilimumab, an inhibitor of CTLA-4 signalling, improves median OS when combined with a peptide vaccine (glycoprotein 100) from 6.4 to 10.0 months, when compared to treatment with vaccine alone.³² Other T cell coinhibitory receptor targeting agents have been developed and have shown promising results. An early phase trial studying an anti-programmed death 1 (PD-1) monoclonal antibody in NSCLC has shown encouraging response rates and an acceptable side effect profile.³³

Cervical cancer is intimately associated with infection by the human papillomavirus (HPV), particularly subtypes HPV-16 or HPV-18. Cervical carcinomas contain HPV DNA integrated into the host cell genome, and two viral oncogenes, E6 and E7, are implicated in 90% of cases. HPV E6 induces accelerated proteasomal degradation of p53, while E7 binds and degrades the pRB retinoblastoma tumour suppressor protein.³⁴ This affects the tumour signalling and growth control of cells. Various strains of the virus have been linked to cancer, in particular cervical, anal and head and neck cancers. The FUTURE (Females United to Unilaterally Reduce Endo/Ectocervical

Disease) II trial randomised use of an HPV vaccine in 12 167 women between the ages of 15 and 26 years. In those not previously infected with the HPV-16 or HPV-18, there was a lower incidence of high-grade cervical intraepithelial neoplasia (CIN) and a reported vaccine efficacy against high-grade CIN of 17%.³⁵ Since September 2008, there has been a national vaccination programme for girls aged 12–13 years. As cervical cancer is one of the leading causes of cancer-related death in developing countries, a worldwide vaccine programme would reduce cervical cancer risk on a global scale.

For patients with metastatic prostate cancer, there is an option to use immunotherapy which has recently been approved by the FDA. The sipuleucel-T is a vaccine that uses autologous peripheral-blood mononuclear cells and activated antigen-presenting cells to stimulate an antitumour response. The IMPACT (Immunotherapy for Prostate Adenocarcinoma Treatment) study demonstrated a survival benefit of 4.1 months in sipuleucel-T group (25.8 months) compared to placebo (21.7 months).³⁶

PROGRESS IN HORMONAL TREATMENT

Androgens, oestrogens and progestins modulate the normal development of cells within the breast and prostate, while in the neoplastic cell these sex steroid hormones perpetuate growth. Although this does not correspond to a hallmark of cancer, hormones are required to perpetuate cancer cell growth, and the antihormonal agents were one of the first targeted agents in cancer drug development. These drugs spare the normal functions of the cell while depriving cancer cells of its important growth stimulus. Well known examples include oestrogen receptor modulators (eg, Tamoxifen) and aromatase inhibitors (eg, Letrozole), which have been beneficial in women with oestrogen receptor positive breast cancer. Hormonal therapy in breast cancer is relevant at all points in the treatment course, in the initial stages of management after surgery and in the metastatic setting.

Due to its dependence of prostate cancer on testosterone to drive cell growth, treatment has relied heavily on hormonal agents that cause chemical castration. Luteinizing hormone releasing hormone (LHRH) analogues, such as goserelin, have been the mainstay of this for many years, however, it is common for resistance to emerge against. In such cases, termed castration-resistant prostate cancer, inhibition of a microsomal enzyme involved in androgen and oestrogen biosynthesis (Cytochrome P17) offers a new option for treatment. This inhibitor, Abiraterone, is well tolerated and has antitumour activity in combination with prednisolone in this population of heavily pretreated men.³⁷ At 12.8 months follow-up, median OS was longer in the abiraterone–prednisone group than in the placebo–prednisone group (OS=14.8 vs 10.9 months).³⁸

BIOLOGICAL APPROACHES ON THE HORIZON

Predicting resistance

Knowledge of signalling pathways can clarify the way in which drug resistance develops. The resistance patterns and compensatory upregulation of neighbouring pathways found are new potential drug targets. For example, acquired resistance to erlotinib develops in many ways, including amplification of the tyrosine kinase receptor, mesenchymal epithelial transition (MET), and the development of secondary (T790M) mutations in the EGFR kinase domain.³⁹ These discoveries have led to the development of T790M-targeted agents, as well as the combination use of erlotinib and MET inhibitors.⁴⁰

THE ERA OF PERSONALISED MEDICINE

The development of novel technologies in parallel with advances in understanding of the molecular biology of cancer has empowered researcher and clinician to examine the whole genome, transcriptome, proteome and metabolome. These high-throughput tools allow a better understanding of the cancer cell and, thereby, identify biomarkers which can be applied to new and existing drug targets.^{41–42} Technological advances in obtaining and processing tumour samples will be crucial in the development of personalised cancer treatment. The BATTLE (Biomarker-integrated Approaches of Targeted Therapy for Lung Cancer Elimination) trial demonstrated the feasibility of individualised lung cancer treatment through the use of biomarkers and tumour profiling to ensure appropriate molecular targets are correctly treated.⁴³ On this basis, the future of oncology does not lie in applying a generic drug to every patient, but instead identifying the specific tumour biology within an individual to achieve the best possible treatment.

THE OTHER HALLMARKS AND DRUG DEVELOPMENT

Knowledge about the phenotypic characteristics of cancer has enabled us to design drugs against these specific features. Despite these advances, there are certain hallmarks of cancer that are elusive targets or have yet to yield an effective treatment. For example pro-apoptotic mimetics have been developed in an attempt to overcome the cancer cell's resistance to programmed cell death, and although there are promising in vitro results, human studies demonstrating benefit are lacking.⁴⁴

Anti-inflammatory drugs, such as the cyclo-oxygenase-2 (COX-2) inhibitor celecoxib have shown a small but significant benefit in a variety of tumours, such as lung, breast and colorectal cancer.⁴⁵ Whether this result is wholly due to anti-inflammatory effects is not clear, however, as these agents also affect pathways responsible for angiogenesis and apoptosis.

THE CHALLENGES OF DRUG DEVELOPMENT IN CANCER

Although chemotherapy is still standard-of-care in the treatment of most cancers, biological targeted agents are increasingly commonly used in the clinical setting. However, for every biological agent that gets a license, there are many more that fail after initial trials. The costs and risks of taking a drug from the laboratory bench to the patient's bedside are enormous. The advent of personalised medicine means that the patient population that is actually suitable for each drug will probably continue to get smaller all the time. This raises difficult but important questions about how drugs are developed, tested and funded. Although the future of cancer treatment will rely on an integrated approach between scientists and clinicians using cutting edge technology to identify novel targets and design the relevant drugs, the more prosaic issue of money will be equally important.

Main messages

- ▶ Understanding tumour biology and the hallmarks of cancer has led to development of new drugs in oncology.
- ▶ New drugs consist of immunomodulatory agents and drugs that target proliferation, angiogenesis and growth-signalling pathways.
- ▶ Targeted therapies can be used as single agents or in combination with chemotherapeutic agents and radiotherapy in some cases.

Current research questions

- ▶ Are overall survival and progression-free survival the best primary endpoints to use when targeted therapies are trialled?
- ▶ Will our better understanding of tumour immunology and use of novel immunomodulatory agents lead to the widespread introduction of immunotherapy for cancer?
- ▶ If chemotherapeutic agents are considered cytotoxic, whereas a large number of targeted agents are cytostatic, what is the best method of assessing tumour response?

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Self assessment questions

Answer true (T) or false (F) for the below:

1. PARP inhibitors are drugs that have been developed for use in breast and ovarian cancer as this is a target for patients that express the BRCA 1/2 mutation.
2. Vemurafenib is an inhibitor of the BRAF V500E mutation, which is licensed for use in metastatic melanoma.
3. Cardiotoxicity is a side effect of Trastuzumab, therefore, echocardiograms are required every 3 months to monitor these effects.
4. Her3 is a homodimer, and therefore, has no ligand.
5. Erlotinib is licensed for first-line use in lung cancer, but only in patients with EGFR mutations.

Competing interests None.

Provenance and peer review Commissioned; externally peer reviewed.

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Answers

1. T
2. F
3. T
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5. F